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10/052,362	01/18/2002	Mu-III Lim	CP-1218	3380

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EXAMINER

TUCKER, ZACHARY C

ART UNIT

PAPER NUMBER

1624

DATE MAILED: 10/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

	Application No. 10/052,362	Applicant(s) LIM ET AL.	
<b>Office Action Summary</b>	Examiner Zachary C. Tucker	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 11 September 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) 11-24 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-10 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>3</u> | 6) <input type="checkbox"/> Other:  |

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## DETAILED ACTION

### *Restriction Requirement*

Applicant's election without traverse of Group I (claims 1-10) in Paper No. 6 is acknowledged.

Claims 11-24 are withdrawn from further consideration pursuant to 37 CFR

1.142(b) as being drawn to a nonelected invention.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the definition recited for the substituent  $R^3$  and  $R^4$  includes, "...or  $R^3$  and  $R^4$  together form a  $C_1$  to  $C_5$  alkylene group;"  $R^3$  and  $R^4$  *cannot* together form a  $C_1$  alkylene group – the smallest alkylene group possible when  $R^3$  and  $R^4$  together form said alkylene group is a  $C_2$  alkylene group – if  $R^3$  and  $R^4$  were reduced to one carbon atom, there would be no alkylene group present.

Because claims 2-10 all depend either directly or indirectly from claim 1, which is found to be indefinite, claims 2-10 are therefore also indefinite under 35 U.S.C. 112, second paragraph and are rejected under that statute as well.

Claim 1 has been examined on the merits as though the definition of  $R^3$  and  $R^4$

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recited "...or R<sup>3</sup> and R<sup>4</sup> together form a C<sub>2</sub> to C<sub>5</sub> alkylene group;" instead of "...or R<sup>3</sup> and R<sup>4</sup> together form a C<sub>1</sub> to C<sub>5</sub> alkylene group;"

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coleman et al, "NICOTINE-LIKE STIMULANT ACTIONS OF SEVERAL SUBSTITUTED PHENYLCHOLINE ETHERS" The Journal of Pharmacology and Experimental Therapeutics, vol. 148(1), pages 66-70 (1965) in view of Organic Chemistry, Paula Yurkanis Bruice, © 1995 Prentice Hall, pages 588-591.

The Coleman et al reference discloses a compound O-(3-aminophenyl)choline bromide, amongst 6 other phenylcholines (see Table 1 and Table 2), and discusses some structure activity relationships in this series.

At the time the invention was made, the compound of claims 1-6 wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each a methyl group would have been obvious to one of ordinary skill in the art, given the teaching of Coleman et al.

The deficiency of the Coleman et al reference is that Coleman et al discloses the compound according to formula (1) of claim 1 except for the required at least C<sub>1</sub> alkyl (methyl) groups on R<sup>3</sup> and R<sup>4</sup>.

Coleman et al states that of particular importance in the determination of a compound in the series' relative potency in stimulation of the nicotinic receptor as measured by the compounds' vasopressor effect in cats and dogs is the inductometric effect of the *meta* substituent on the phenyl ring. The most potent compound was the 3-iodo derivative, the second most potent was the 3-amino derivative (Table 2).

On page 68 (first column), Coleman et al states that the halogens and the NH<sub>2</sub> groups are, in addition to being electron withdrawing, "are also electron-releasing through resonance," but that when these groups are in the 3-position, this effect is absent or markedly reduced.

One of ordinary skill in chemistry is aware that the overall effect that certain phenyl substituents have is the sum of the substituent's electron-donating effect and electron withdrawing effect.

As demonstrated in Organic Chemistry, Bruice, © 1995 by Prentice Hall, pages 588-591, on page 590 (table 13.1) the NH<sub>2</sub> group is the most strongly activating (that is, most strongly electron withdrawing) of the phenyl substituents in Coleman et al's compounds (all of the phenyl substituents exemplified by Coleman et al are shown in Bruice's table 13.1).

On page 588 of the Bruice text, it is explained that for the '*strongly activating substituents*', the net electronic effect on the aromatic ring that the substituent has is the sum of the substituents' electron donating effect through resonance and electron-withdrawing effect through induction. The Bruice text states that for the '*strongly*

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*activating substituents*' in table 13.1, the resonance effect (electron donating) is much stronger than the inductive effect (electron withdrawing).

It may be seen from table 13.1 that  $\text{NR}_2$  is less activating than  $\text{NH}_2$ , therefore there must be a greater inductive effect from the dialkylamino substituent than from  $\text{NH}_2$  if the net effect is the sum of the inductive and resonance effects.

Coleman et al states that for the 3-substituted compounds disclosed in that reference, the resonance effects of the substituent are negligible or absent (page 68, first column). Thus, the *inductive effect* of the 3-substituent is what plays a role in increasing or decreasing the compound's potency as a nicotine-like stimulant.

Therefore, if the 3-amino substituted phenylcholine ether's potency is due to the amino group's inductive effect (and not the electron-donating effect through resonance), and if the  $\text{NR}_2$  group possess more of this character than  $\text{NH}_2$ , one of ordinary skill in the art would expect the 3-dialkylamino phenylcholine ether to be at least as if not more potent as the 3-iodo- phenylcholine derivative.

Coleman et al states on page 68 that it is not purely the 3-substituent's inductive, electron-withdrawing effect that determines the potency, else the 3-nitro derivative would be expected to be the most potent instead of the least potent, as was determined experimentally. Coleman et al teach that it is the inductometric effect that the 3-substituent has, which refers to the inductive effect along the substituent and ring bond only at the moment of interaction of the molecule with a second molecular system. This

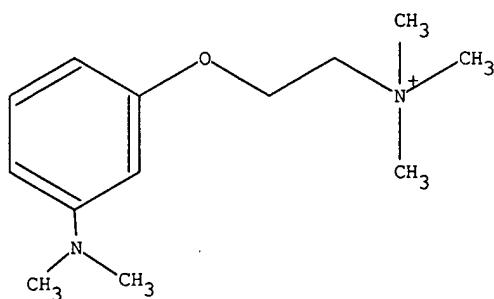
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generally depends on the electronegativity of the substituent (page 68 second column), that is, how easily the substituent's electrons are displaced.

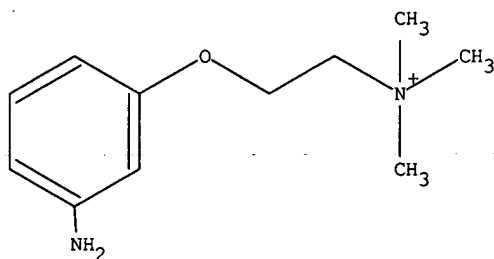
Coleman et al, in the discussion on page 68, from the bottom of the first column and on to the second column, teaches that the polarizability of the 3-substituent is directly proportional to the compound's activity.

A dialkylamino group possess easily displaceable non-bonding  $\pi$ -electrons, as opposed the nitro group's permanently charged nitrogen and oxygen atoms. A dialkylamino group also has greater inductive effect on an aromatic ring than an amino group, as is demonstrated by its lesser degree of overall electron-donating (resonance) effect, as demonstrated by table 13.1 in the Bruice text.

One of ordinary skill in the art would therefore conclude from the Coleman et al reference and the excerpt from the Bruice text that a compound having the structural formula:



is a more potent nicotine like stimulant than:



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due to the increased inductometric polarizability of the 3-dimethylamino substituent as compared with a 3-amino substituent in the compounds disclosed by Coleman et al.

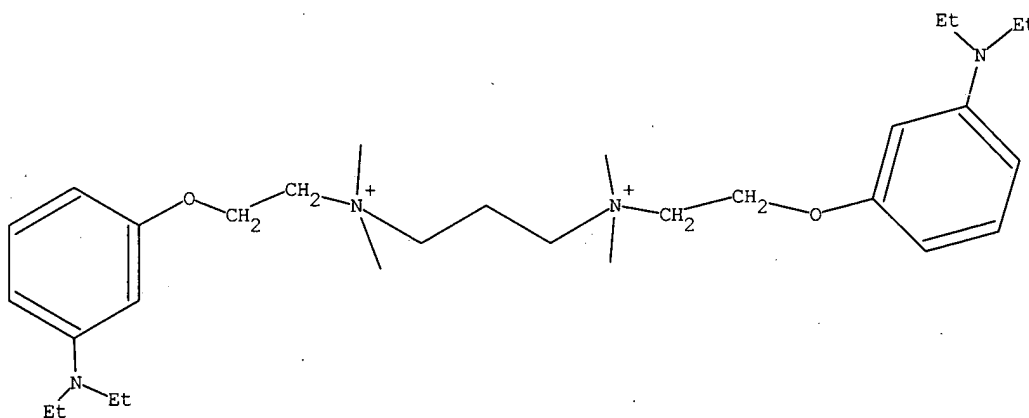
The motivation to thusly modify Coleman et al's 3-amino (to 3-dimethylamino) compound would have been to make potent nicotine-like cholinergic drugs.

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### ***Cited of Interest***

US 3,755,287 (Hegar et al) is cited of interest, as it discloses a compound similar to a compound according to structural formula (1) in instant claim 1.

Procedure VII, in column 20 of Hegar et al describes synthesis of a *bis*-quaternary ammonium compound from 2 moles of 3-diethylamino-2'-dimethylaminoethyl ether and 1 mole of 1,4-dibromobutane, having the structural formula depicted below.



### ***Allowable Subject Matter***

Claims 7-10 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

The process according to claims 7-10 is not suggested in the Coleman et al reference.

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**Conclusion**

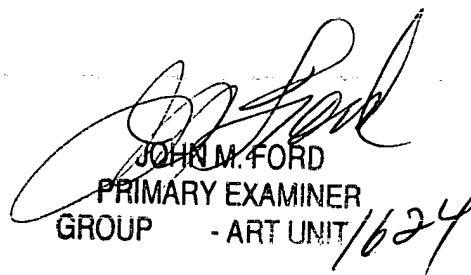
Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (703) 305-2050. The examiner can normally be reached Monday-Friday from 7:00am to 3:30pm. If Attempts to reach the examiner are unsuccessful, the examiner's supervisor, Mukund Shah, can be reached at (703) 308-4716. The fax number for the organization where this application or proceeding is assigned is (703) 308-4556 for regular communications and (703) 308-4242 for after-final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

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JOHN M. FORD  
PRIMARY EXAMINER  
GROUP - ART UNIT 1624